D1040B

1/27

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office
HFL-35
60 8th Street, N.E.
Atlanta, Georgia 30309

11/20

November 7, 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Donal J. Geaney
Chairman and CEO
Elan Corporation plc
Monksland, Athlone
County Westmeath
Ireland

WARNING LETTER

Dear Mr. Geaney:

An inspection of your drug manufacturing facility located in Gainesville, Georgia, was conducted between August 25 and September 17, 1997, by Investigator Robert L. Lewis, Chemist Penny H. McCarver, and Chemist Daphne Santiago. Our investigator and chemists documented several significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause your drug product, Verelan, to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

You have failed to appropriately investigate and respond to out of specification (OOS) analytical results. Numerous inconsistencies were noted in the handling of data and the decisions made in response to these OOS results. You have failed to maintain adequate documentation to substantiate the invalidation of OOS results obtained during dissolution and assay testing of in process and finished product. When investigations were conducted, explanations could not always be substantiated or were incongruent. The assumptions made as to the reason for the OOS results were speculative at best, based on the supporting documentation available. We are concerned that your OOS investigation methodology and the conclusions made have concealed true product quality problems.

The dissolution checklist for lot 6L331 (2 month test station) attributed failed dissolution results to "air bubbles", although the same checklist also states that no debris or air bubbles were seen in the sample lines. Laboratory Investigation Report (LIR) 97-06-05 states "No problems were noted" following an initial investigation of low dissolution results. The investigation conducted later in response to another low value concluded that the filter was clogged. The second conclusion was made by a different analyst. We were informed that your management had

found other instances where analysts other than those performing the actual analysis were documenting the investigation and conclusion. LIR 96-09-12 concluded that the "possibility exists that some material was lost during transfer however...this is doubtful". The investigation ended at this point, however.

LIRs 97-06-08 and 97-05-12 attribute low dissolution results to nondescript "debris" in the equipment. The reports stated that the debris "cleared itself" at later timepoints as evidenced by acceptable results being obtained. There is no clear indication or documentation available that the debris was ever actually observed. Your firm could provide no studies or analytical data to indicate the actual effect of line debris on dissolution results. Similarly, your firm could not provide any documentation as to the effects of air in the dissolution system on analytical results. LIRs were noted to attribute both high dissolution results and low dissolution results to air bubbles. The effect of air or debris in the system has never been definitively established by your firm.

You had failed to establish appropriate procedures for the evaluation of OOS and atypical laboratory results. The procedures failed to include information about the investigation of aberrant dissolution and content uniformity results. Although the overwhelming majority of the laboratory investigations during this period related to dissolution runs, the procedure did not address steps to investigate anomalous dissolution results. This included a failure to even mention Form #33, dissolution checklist, which has been used in lieu of the formal LIR. You have failed to implement a system for confirming the implementation of the proposed corrective actions taken in response to OOS results. This included a lack of documentation that corrective actions listed in LIRs were actually performed.

Prior to the initiation of this inspection there was no attempt to evaluate OOS results to detect trends in analyst errors in the laboratory as part of an ongoing evaluation of the effectiveness of analyst training. Since January 1996 there have been more than [redacted] analyst errors documented as resulting in OOS results and retesting of samples. This is of particular concern due to the conspicuous turnover rate of laboratory analysts over the past two years. This turnover rate also raised the question as to the adequacy of training for these analysts. Training deficiencies could have been a source of the inconsistencies observed in the handling of and response to OOS results.

You failed to respond to calibration failures of the ultraviolet (UV)/visible spectrophotometer as required by your procedures. Instruments were not taken out of service, logbooks did not reflect passing/failing calibrations, certificates of calibrations were incomplete, there was no investigation into the cause of failures and no record was maintained of the corrective action taken as required. The procedures for maintaining the dissolution equipment were inadequate to prevent frequent equipment malfunctions. Chronic problems such as valve blockages, actuator problems, air bubbles, filter clogs and software problems were noted on a recurrent basis over the past 18 months. The dissolution equipment with model [redacted] spectrophotometers have remained in use over the past 18 months although this model was identified by your firm in January 1996 as the cause of numerous OOS results due to frequent malfunctions. The continued malfunction of these units has impeded quality control procedures and monitoring.

You failed to properly validate the dissolution testing equipment. There was no raw data available for the installation qualification/operation qualification (IQ/OQ) for three of the spectrophotometers used in dissolution testing. Qualification data could also not be found for system [redacted] Systems [redacted] and [redacted] were placed into service prior to execution of IQ/OQ protocols. Although the spectrophotometer in system [redacted] failed photometric accuracy during IQ/OQ, this was not noted in the final approved report. There also were no procedures addressing qualification and/or calibration of dissolution equipment following changes in major components (such as UV lamps and computers).

You had failed to show that the automated sampling probe filters used in the dissolution apparatus vessels were inert as required by the United States Pharmacopeia (USP). You failed to calibrate the spectrophotometers for photometric accuracy in the UV region which is also a USP requirement. Verapamil Hydrochloride absorbs in the UV region. The dissolution medium deaeration technique had not been properly validated.

Several significant deficiencies were noted in the Verelan Dissolution Method Validation Study (Phase 1). Attempts to corroborate data in the validation report with supporting raw data in the laboratory were difficult and frustrating for the FDA personnel conducting the inspection. Some data reported in the validation could not be substantiated with accompanying laboratory records and in many cases the data was a source of confusion for our investigator and chemists. OOS accuracy results reported by analyst 3 were never submitted in the final report. Repeat analysis performed on a different system passed specifications and these results were submitted in the report. No data was available supporting the dissolution results tabulated in the final report for the 1 hour, Multi-Component Media w/Fumaric Acid test (Analyst 3). Raw data was not adequately identified or traceable to results noted in the report. Raw data and calculations were not checked by a second responsible individual as required by your procedures. Inaccurate calculations were noted in the report.

These findings by FDA prompted the management at Gainesville to commit to revalidate the dissolution method. This does not negate the fact, however, that management had previously signed off and approved the seriously deficient original validation report.

You have failed to establish temperature and humidity specifications for the timing and application rooms. You also could provide no data to support the [redacted] hour specification for the holding of timed beads in an uncontrolled environment.

Many of the above deviations were included on the FDA 483 (Inspectional Observations) which was issued to and discussed with Dr. Arlene Ocampo, Vice President Operations, at the conclusion of the inspection. A copy of the FDA 483 is enclosed for your review. The violations noted in this letter and in the FDA 483 are symptomatic of serious underlying problems in your firm's quality assurance systems. The deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. It is your responsibility to ensure adherence to each requirement of the Act.

You are responsible for investigating and determining the causes of the violations identified by FDA. You should take immediate actions to correct these violations. Failure to promptly correct these deviations may result in legal sanctions provided by the law such as product seizure and/or injunction, without further notice to you. Federal agencies are advised of the issuance of all warning letters involving drugs so that they may take this information into account when considering the award of contracts.

We are cognizant of the fact that corrective actions have been implemented at Elan in response to our most recent inspection. We have received and reviewed the formal response to the FDA 483 prepared by Dr. Ocampo. Our review of that response would indicate that your firm is clearly headed in the right direction in addressing the FDA 483 observations. A more detailed response with our review findings will be forthcoming. We are also aware that many of these problems had been previously identified by your firm which had resulted in additional corrective measures being taken. We are mindful of the positive comments expressed during the September 24 meeting at the District Office with Mr. Mulligan, Dr. Ocampo, Ms. Schuster, and Dr. Hamm. We also appreciated the opportunity to discuss the inspectional findings with you at the District Office yesterday and the commitments expressed to implement corrective action. Taking all of these factors into account, we still made the decision to issue this letter to Elan due to our continued concern about the nature and scope of the inspectional findings.

A Warning Letter was previously issued to your firm in October 1995. Although those deviations were corrected, we now find significant problems again at the Gainesville facility. We also are concerned that although problems were identified in the laboratory internally, the initiation of corrective action was done in a less than timely manner. You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of any additional steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely,

Ballard H. Graham, Director
Atlanta District

cc: Dr. Arlene Ocampo
Elan Pharma, Inc.
1300 Gould Drive
Gainesville, GA 30054